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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/783,848
Filing Date: February 20, 2004
Appellant(s): DE BRABANDER ET AL.

Steven M. Reid
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 3, 2008 appealing from the Office action mailed April 22, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the second brief of February 4, 2009 is correct.

This appeal involves claims 7-12, and 23.

Claims 3, 6-12, 14, 17, 23-24, 26-28 are pending.

Claims 14, 17, 24, 26-28 are withdrawn.

Claim 3 is allowed.

Claims 6-12, 23 are rejected under 112 1st paragraph.

Claims 6-12, 23 are rejected under 112 2nd paragraph.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

Liao et. al. "Total Synthesis and Absolute Configuration of the Novel Microtubule-Stabilizing Agent Peloruside A" *Angewandte Chemie International Edition* **2003**, *42*, 1648-1652.

Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358.

Jimenez-Barbero, J. et. al. "NMR Determination of the Bioactive Conformation of Peloruside A Bound To Microtubules" *Journal of the American Chemical Society* **2006**, 128, 8757-8765.

Pineda, O. et. al. "Computational comparison of microtubule-stabilising agents laulimalide and peloruside with taxol and colchicines" *Bioorganic & Medicinal Chemistry Letters* **2004**, 4825–4829.

Gaitonos et. al. "Peloruside A Does Not Bind to the Taxoid Site on β-Tubulin and Retains Its Activity in Multidrug-Resistant Cell Lines" CANCER RESEARCH August 1, 2004, 64, 5063–5067.

Hamel et. al. "Synergistic Effects of Peloruside A and Laulimalide with Taxoid Site Drugs, but Not with Each Other, on Tubulin Assembly." *Molecular Pharmacology* **2006**, *70*, 1555–1564.

Manon T. Huizing "Tubulin interacting agents" in Drugs Affecting Growth of Tumours Herbert M. Pinedo Carolien H. Smorenburg, Eds.; Birkhäuser Verlag: Basel, 2006 pg. 101-132.

Altmann et. al. "Epothilones and related structures a new class of microtubule inhibitors with potent in vivo antitumor activity." *Biochimica et Biophysica Acta* **2000**, *1470*, M79-M91.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-12, 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellants regards as the invention. The term "functionalized alkyl", "functionalized alkenyl" etc. is indefinite. Unless one knows what a substituent is a determination of what these compounds are cannot be made. The specification does not fully elaborate the identity of these substituents. This rejection is not being made for

breadth, but for an inability to ascertain what this functionalization is. The claim amendments of February 12, 2009 do not overcome this rejection, but rather state that:

> wherein **each functionalized group is substituted with** ~~the functional group is a heteroatom,~~ a halide, an aryl, or a heteroaryl.

It is still unclear what the "functionalized group" is, and the new definition suggests that these "functionalized" groups are further substituted with halide, an aryl, or a heteroaryl.

Claim Rejections - 35 USC § 112 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-12, & 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a few compounds, it does not reasonably provide enablement for the prophetic genera. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and

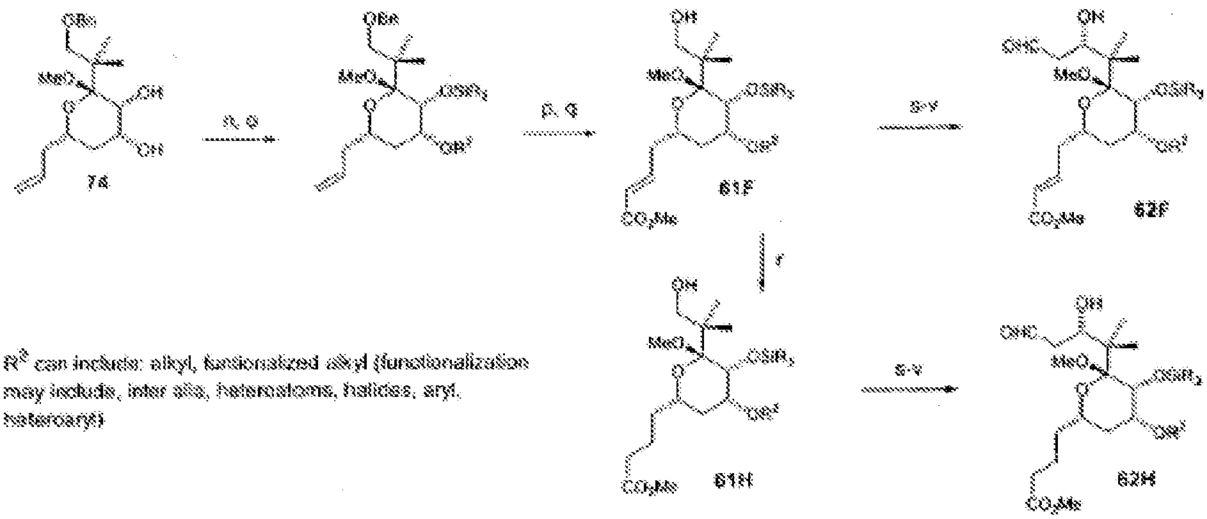
(H) The quantity of experimentation needed to make or use the invention
In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of heterocycles, prophetic modifications bearing multiple substitutions. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist/medicinal chemist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. As stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally

> planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)……………….." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention: Certain limitations of the chemistry used to prepare the examples, and the proposed prophetic examples is readily apparent. Claims 7-12, 23 have claims drawn to Peloruside compounds that lack the OR_4 or OR_6 moiety of structure 65D, claim 23, these are compounds like the olefin 65F & 65 E and the alkane 65G. However it is very clear that simply plugging in what are the analogous starting materials into the synthesis of Peloruside (which is the only example of the instant case) will not allow for their preparation. The prophetic reaction scheme of Figure 90 is illustrative of this clear failure. The olefin of compound 61F will be dihydroxylated and subsequently cleaved when treated with the conditions of s-v.



Reagents and conditions: n) base, R_8X; o) TESOTf, 2,6-lutidine; p) LiDBB, THF or Li, naphthalene, THF; q) Ru-alkylidene catalyst (cross metathesis); r) conjugate reduction; s) oxidation to aldehyde; t) allylBEt_2; u) cat. OsO_4, NMO; v) $Pb(OAc)_4$. PMB = p-methoxybenzyl, TES = triethylsilyl, NMO = 4-methylmorpholine-N-oxide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, LDA = lithium diisopropylamide, mCPBA = m-chloroperbenzoic acid, Bn = benzyl.

Figure 90

A more disturbing feature of the instant claims is the inclusion of a laundry list of Groups for R_8, since R_8 necessarily depends on the aldol reaction of ketones analogous to **6** with compound **23** in a key , however none of these reactions have been performed. It is impossible to evaluate the full scope since R_8 is not defined clearly. Taking a closer look at the published account of this synthesis Liao et. al. “Total Synthesis and Absolute Configuration of the Novel Microtubule-Stabilizing Agent Peloruside A” *Angewandte Chemie International Edition* **2003**, *42*, 1648-1652, and comparing it side by side to the disclosure (shown on the next page) it is clear that prophetic synthesis or paper chemistry is far from straightforward and highly unpredictable.

Application Text

Peloruside analogs.

[0077] An example for the synthesis of analogs with C9-C 11 hydroxyls protected as a cyclic acetal is provided below. The biologically active forms of these analogs will have an enantiomeric relationship to the ones drawn in the schemes below. Union of fragments 6 and 25 and completion of a Peloruside analog is shown in Scheme 8 below. *Mukayama-type aldol reaction of aldehyde 25 with the enolsilane derived from methyl ketone 6 (BF3"Et20, CH2C12, -78°C) afforded almost exclusively (14:1) the 1,3-syn aldol product. This stereochemical outcome is contrary to the outcome expected from extensive literature precedents. Evidence provided below however, indicates that aldehyde 25 entered this reaction with an unprecedented bias for the formation of the 1,3-syn fl-hydroxy ketone 26 (80% yield). Hydroxy ketone 26 was protected as C13 methyl ether 27, followed by CBS reduction (and ester hydrolysis to reach seco-acid 28. Slow addition of this compound to a premixed solution of PPh3 and diisopropylazodicarboxylate* instigated formation of macrolactone 29 in 40-50% yield. *The stereochemistry of 29 was deduced based on a series of NOE correlations that locate H11, H13 and H15 on the same upper side of the macrolactone ring in agreement with the assigned C 13(S) configuration*. The synthesis of 29 provides an example of Peloruside spiroacetal analogs, i.e. Peloruside macrocycles that have the C9 and C 11 hydroxyl groups incorporated into an acetal ring, and can be prepared according to the general outline of Scheme 8. Note that enantiomeric 29, i.e. ent-29, and analogs will be biologically active.

Liao et. al.

With fragments 6 and 25 (derived from 24 as shown) at hand**, their union and completion of the peloruside macrocycle seemed an attainable goal, yet unexpected surprises lay ahead (Scheme 4).** *Mukaiyama-type aldol reaction of aldehyde 25 with the enol silane derived from methyl ketone 6 afforded almost exclusively (14:1) the compound that was assumed to be the expected 1,3-anti aldol product based on extensive literature precedent.[15] Evidence provided below, however, indicates that aldehyde 25 entered this reaction with an unprecedented bias for the formation of the 1,3-syn bhydroxy ketone 26 instead (80% yield). Initially unaware of this stereochemical outcome, we continued with methyl ether formation (!27), CBS reduction,[16] and ester hydrolysis to reach seco-acid 28. Slow addition of this compound to a premixed solution of PPh3 and diisopropylazodicarboxylate instigated formation of macrolactone 29 in 40–50% yield.[17]* We were able to deduce *the stereochemistry of 29 based on a series of NOE correlations that locate H11, H13, and H15 on the same upper side of the macrolactone ring in agreement with the assigned C13(S) configuration* (Figure 1). At this point, we were left with the obvious challenge of correcting the stereochemistry at C13. **Various attempts to remove the (2-naphthyl)methylidene acetal failed.[18] Undeterred, we embraced the opportunity to explore a more attractive avenue that would eliminate this protecting group problem altogether, that is, we decided to advance materials with a free C11 alcohol through the remainder of the synthesis.**

While the synthesis is one aspect, in this case these compounds bear no structural resemblance to one another when the acetals and "functionalized" compounds are considered and even if they did the situation is far from clear that they would have the desired activity. As one reviewer stated, Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358:

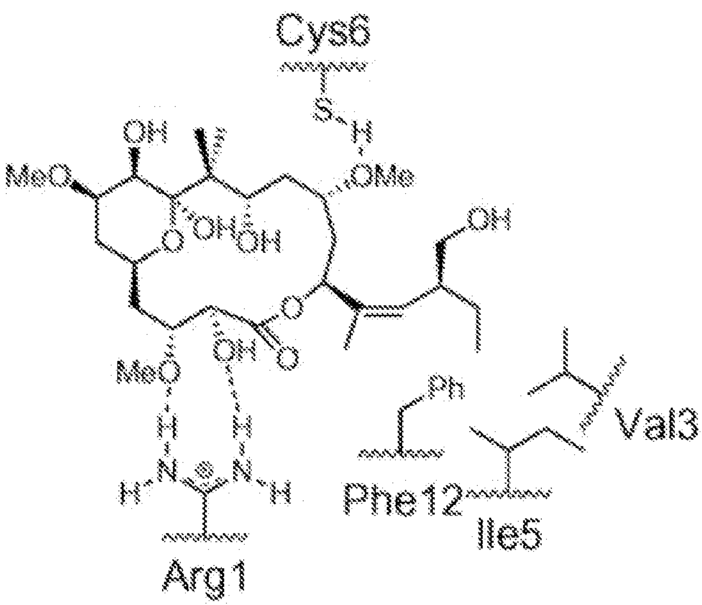
> "….. compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.[15] In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure…(pg. 4536 column 2, line 9)…..This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at ≥ 0.85 Tanimoto similarity in Daylight fingerprints, **only 30% of compounds similar to an active are themselves active**."(conclusions)

In this instance we have no working examples for the majority of the claims and as stated by Jimenez-Barbero, J. et. al. " NMR Determination of the Bioactive Conformation of Peloruside A Bound To Microtubules" *Journal of the American Chemical Society* **2006**, 128, 8757-8765, conclusions pg. 8763 :

Nevertheless, despite the large size of the macrocyclic ring, intramolecular interactions within the Peloruside A ring strongly affects the conformational features of this molecule, which indeed only shows conformational mobility around a fairly narrow part of the molecule. **Specifically, van der Waals contacts and torsional constraints strongly bias its conformational behavior.** Yet, this existing conformational freedom, in the presence of a given solvent, serves to modulate the presentation of polar and nonpolar surfaces to interact with the binding site. **Indeed, according to our experimental data, only one of the two major conformations existing in the water solution is bound to microtubules,** distinct from that predominantly present in nonpolar (chloroform) solvents. A model of the binding mode to tubulin has also been proposed, which involves the α-tubulin monomer, in contrast with taxol, which binds to the *β*-monomer.

No one would argue that the laundry list of "functionalized" compounds and "heteroaryls" would have activity.

Since few analogs of Peloruside A have been tested to date (only 1) an analysis of the speculative biological activity of these compounds seems appropriate. The mechanism of action of Peloruside A is binding to tubulin at an unknown site, however the theoretical binding site(s) have been modeled and the conformation of the molecule is critical. Another author has proposed the following model for the interaction of Peloruside A with tubilin. Pineda, O. et. al. "Computational comparison of microtubule-stabilising agents laulimalide and peloruside with taxol and colchicines" *Bioorganic & Medicinal Chemistry Letters* **2004**, 4825–4829.



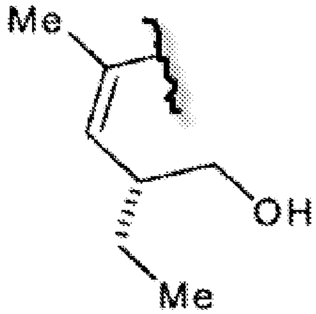
(b)

Thus the conformation of these molecules is critical for activity and in the instant case the compounds of the claims will have an unpredictable effect on the activity and may conformationally restrict the ring of Peloruside. The conformational state of Peloruside A is deemed critical by Jiminez-Barbero et. al. for the molecule to interact with tubulin. The factors

outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

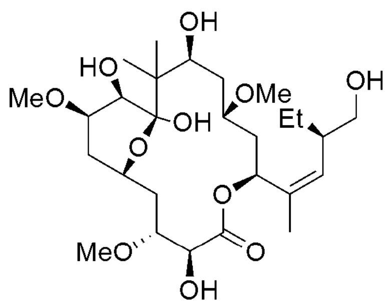
(10) Response to Argument

Appellant's arguments filed on December 3, 2008 have been fully considered but they are not persuasive. The rejections of claims 6-12, 23 under 35 U.S.C. 112 2^{nd} paragraph is maintained. The examiner would like to further clarify that it is not possible to construct any of the working examples from the instant claims. Despite the length of the disclosure, with a great many synthetic intermediates and spectral data, only two compounds were prepared that read on the instant claims, neither of which are under appeal (claim 3 is allowed and claim 6 is also rejected, but has a single example to support it). The examiner would like to initially discuss the rejection under 112 2^{nd} paragraph, as it relates to the rejection at hand because it has an impact the enablement rejection. Appealed claims 7-12, 23 recite the words "functionalized alkyl", "functionalized alkenyl, "functionalized alkynyl", yet no definition is given for these terms. The appellant has attempted to remedy this by adding that each functionalized group is further substituted with "a halide, an aryl, or a heteroaryl". Based on the disclosure, at least for R_8 the only moiety ever shown and can be envisioned as the following group:

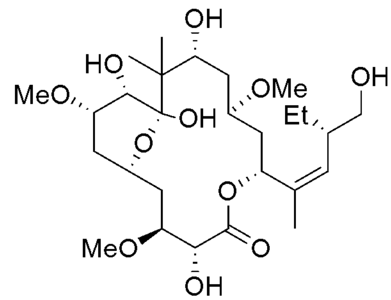


It is not clear how this group can be constructed from the language of the instant claims, as no hydroxy is provided for in the claim language. Thus it would appear that the hydroxy is provided for in the "functionalized" language, since it is not listed as a substituent of further functionalization. This makes it unclear what further modifications are encompassed by the term "functionalized". This has an impact on the enablement rejection, because it is not possible to evaluate the full scope at least where "functionalized alkyl", "functionalized alkenyl, and "functionalized alkynyl" are used.

The enablement rejection of claims 6-12, 23 is maintained for the following reasons, discussed further in the context appellant's remarks. The claims are drawn to analogs of Peloruside A. Peloruside A is a marine natural product shown in Figure 1, below. It is found in the (+) form in nature, and the appellant's specification states on page 12 that the (-) enantiomer is not biologically active.



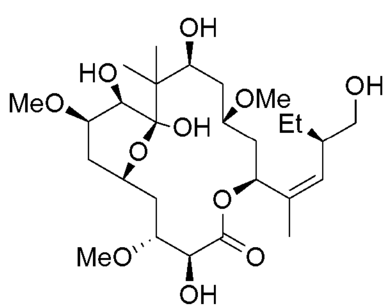
(+)-Peloruside A
BIOLOGICALLY ACTIVE



(-)-Peloruside A
BIOLOGICALLY INACTIVE

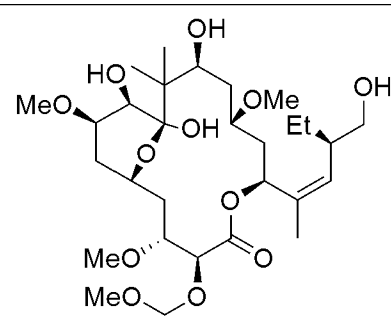
Figure 1. Peloruside A (+) and (-).

Despite the length of the disclosure, which has a great many synthetic intermediates and spectral data, only two compounds were prepared that have biological activity, neither of which read on the instant claims nor are under appeal. These two compounds are shown below in Figure 2.



LX-3111

LX-3111 is (+) Peloruside A



LX-3136

LX-3136 is (+) Peloruside bearing a MOM group.
Compound of allowed claim 3.

Figure 2. The only two working example compounds disclosed which do not read on the appealed claims.

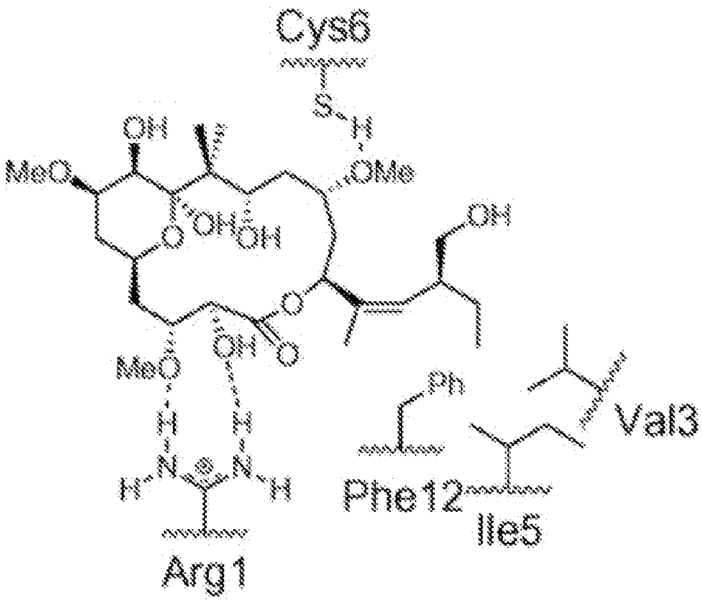
The application renames the known natural compound (+) Peloruside A as LX-3111, and calls the MOM protected compound LX-3136. The application also discloses a naphthyl acetal

which reads on claim 6, shown below, and several silyl protected compounds, none of which read on the appealed claims 7-12, and 23.

The detailed discussion in the rejection for how to make was primarily based on the scope of claim 6, which is not under appeal, and the cyclopropyl compounds of claim 9 (Formula IX) and claim 23 in part (structures 65A, 65C, 65E, and 65I), which while not prepared did have a prophetic synthetic scheme. The other claims, claims 7-8, 10-12, and claim 23 in part, have no syntheses discussed in the specification, thus it is not possible to analyze claims 7-8, 10-12, and claim 23 in a real way for how to make, since there is not even a proposed reaction scheme present to discuss. The rejection for how to make for claims 7-8, 10-12 was not addressed in the affidavit or the appellant's remarks. The examiner has classified the affidavit of Dr. Brabander as that of an expert, not a routineer, however even if such an affidavit is given full weight it does not overcome the rejections of record. The sheer number of required intermediates in the prophetic synthesis is enormous, and even an expert would not regard them as operable. As evidenced by the 112 2nd paragraph rejection a skilled artisan would not know what the scope of the R_8 and R_{16} the variables reciting “functionalized”. Regardless even if the level of skill in the art was that of an expert in synthetic chemistry, and such compounds could be prepared it is not possible to predict which compounds would be useful as anticancer compounds outside of those exemplified. This is because the level of unpredictability in the art is so high.

As has been made of record Pineda, O. et. al. “Computational comparison of microtubule-stabilising agents laulimalide and peloruside with taxol and colchicines” *Bioorganic & Medicinal Chemistry Letters* **2004**, 4825–4829, have modeled the interaction of Peloruside A

with tubulin, the molecular target of Peloruside A action. Pineda reveals several structural features that are critical for the interaction of the Peloruside A with tubulin, in Figure 7b reproduced below.



(b)

In particular the Peloruside A C-13 OMe group interacts with the S-H of the Cys6 of tubulin, the C-2 OH and C-3 OMe interact with the guanidinium group Arg1, and the lipophillic 4-hydroxymethylhexenyl side chain attached to C-15 interacts with the residues Phe12, Ile5 and Val3. The instant claims have abolished these key structural features and present a core that is not known to interact with Peloruside A. Each of the prophetic cores of claims 7-12 are shown below in Figure 3.

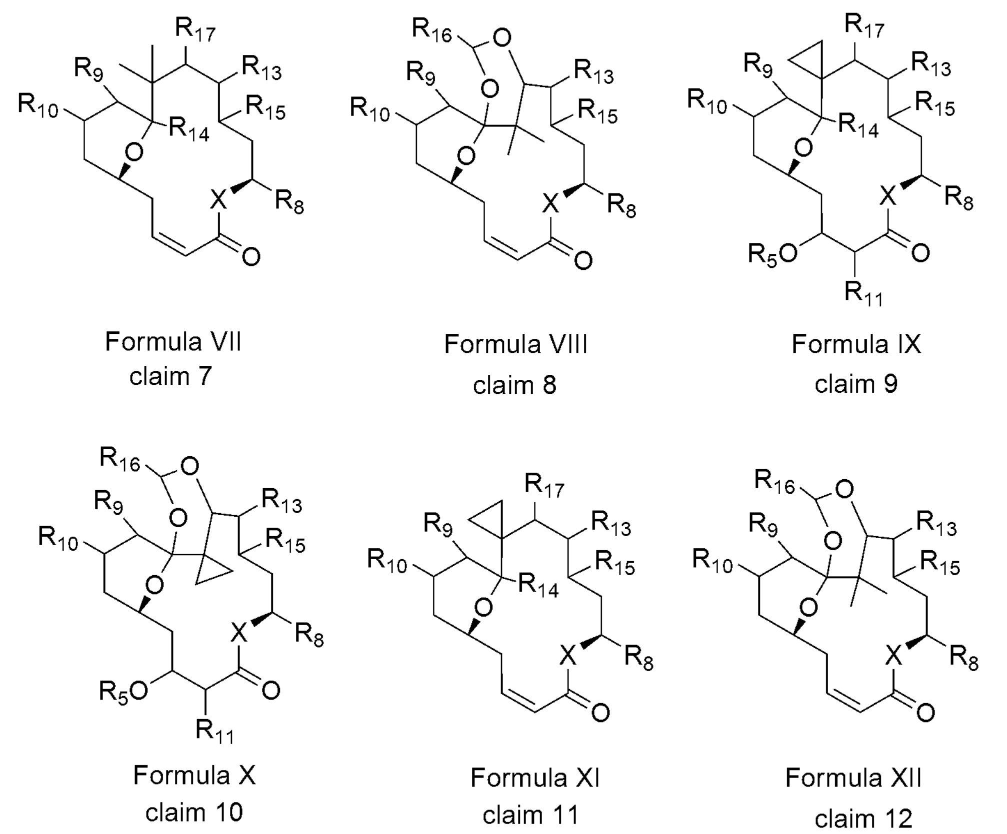


Figure 3. The prophetic cores of instant claims 7-12.

Several key structural features are missing from each of these representations. Prophetic cores of Formula VII, Formula VIII, Formula XI, Formula XII as well as structure 65E and 65F of claim 23, have removed the C-2 OH and C-3 OMe of Peloruside A and replaced it with a lipophillic olefin. Such a replacement will not allow an interaction with the guanidinium group of Arg1 in tubulin. Prophetic cores of structure 65H, 65I and 65J of claim 23, have removed the C-2 OH and C-3 OMe of Peloruside A and replaced these groups with H atom. Such a replacement will not allow an interaction with the guanidinium group of Arg1 in tubulin. Prophetic cores of Formula VII-XII do not possess the 4-hydroxymethylhexenyl side chain

attached to C-15 that interacts with the residues Phe12, Ile5 and Val3 (recites as R_8 in the instant claims). Prophetic cores of Formulae VIII, X, and XII, possess highly strained spirocyclic ring junctions a C-9, which would alter the conformation of Peloruside A. The conformational state of Peloruside A is of course critical for the molecule to interact with tubulin as shown by Jiminez-Barbero et. al., who states that only two conformations are active. The claims are also stereochemically ambiguous with respect to numerous stereocenters. As admitted by the appellants own specification, altering the stereochemistry leads to obliteration of activity (compare (+) Peloaruside A to (-) Peloruside A).

The complete lack of working examples point to the key deficit in the disclosure, namely that undue experimentation would be required to practice the invention and the how to use requirement has not been met. While organic chemistry is highly unpredictable, the degree of unpredictability in the pharmaceutical art is even greater. As one reviewer stated, Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358:

> "….. **compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.**[15] **In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure**…(pg. 4536 column 2, line 9)…..This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at $\geq$ 0.85 Tanimoto similarity in Daylight fingerprints, **only 30% of compounds similar to an active are themselves active**."(conclusions) (Emphasis added)

The examiner is not upholding a rigid scientific standard based in scientific fact, but rather the standard of patent law that the scope of the claims should be commensurate in scope with the

invention disclosed. Claims 7-12, and 23 are entirely prophetic. The appellant has pointed to the Nicholau review to provide support for the prophetic choice of cyclopropyl in place of dimethyl:

> epothilones (K.C. Nicolau *et al. Angew. Chem. Int. Ed.* 37 (1998) 2014-2045). On page 2037, Scheme 38 details the construction of various epothilone libraries that interchangeably employ *gem*-dimethyl and cyclopropyl building blocks designated as compounds 31 and 236, respectively. That is to say, exactly the

The examiner submits that while such a modification to Peloruside A is an area that might be explored in future research, it was not explored here. Making these assumptions about modifications to Peloruside A that would lead to biological activity is not based on sound scientific reasoning. Epothilones and Peloruside A while both tubulin polymerization inhibitors have different mechanisms of action and bind to different sites on the protein: See Gaitonos et. al. "Peloruside A Does Not Bind to the Taxoid Site on β-Tubulin and Retains Its Activity in Multidrug-Resistant Cell Lines" CANCER RESEARCH August 1, 2004, 64, 5063–5067 and Hamel et. al. "Synergistic Effects of Peloruside A and Laulimalide with Taxoid Site Drugs, but Not with Each Other, on Tubulin Assembly." *Molecular Pharmacology* **2006**, *70*, 1555–1564, and Manon T. Huizing "Tubulin interacting agents" in Drugs Affecting Growth of Tumours Herbert M. Pinedo Carolien H. Smorenburg, Eds.; Birkhäuser Verlag: Basel, 2006 pg. 101-132. "The diverse actions of these drugs on microtubules are likely to produce different effects on mitotic spindle function, leading to different effects on cell cycle progression and cell killing." Again while Dr. Brabander, a chemist, believes that these materials look similar "compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether." (Martin ibid.)

The examiner would like to point to the review on the chemical biology of epothilones provided by the appellant in the declaration (Nicholau et. al.). It is clear that a modest selection of derivatives of epothilones were made over many years by armies of chemists that are unarguably some of the most skilled in the world. Moreover, these derivatives clearly have very limited modifications to the macrocycle itself, and these limitations were revealed by detailed studies. See Altmann et. al. "Epothilones and related structures a new class of microtubule inhibitors with potent in vivo antitumor activity." *Biochimica et Biophysica Acta* **2000**, *1470*, M79-M91, the Figure 7 of Altmann is reproduced below:

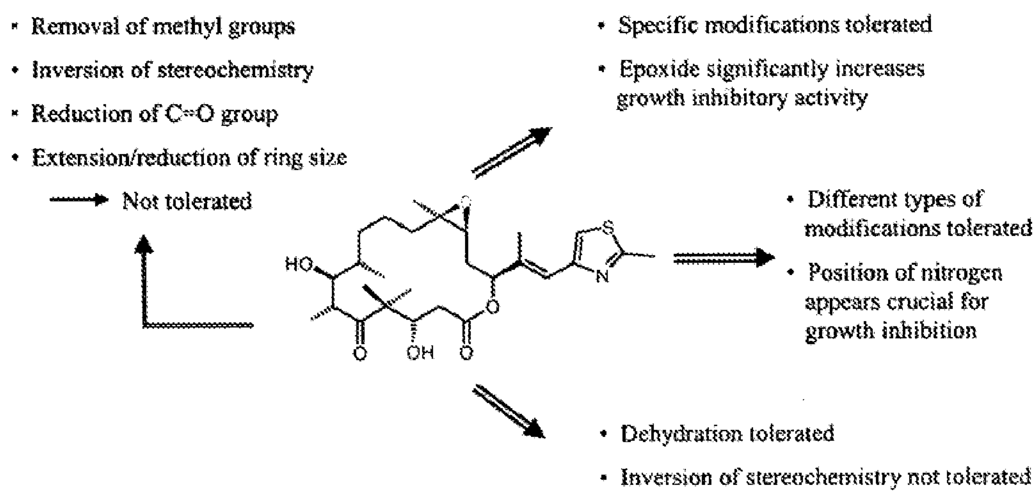


Fig. 7. Structure-activity relationships for epothilones.

The determination of these relationships and the discovery of potent analogs is a different invention, and one that the appellant has not shown to be in possession of. The specification does little but provide broad recitations of broad genera of compounds that might be prepared and tested. While undoubtedly the appellant has provided a useful synthesis of Peloruside A, no trail is blazed to the derivatives. It is neither obvious nor predictable, to make such modifications.

In order to practice the full scope of the invention, one of ordinary skill would not only need to create synthetic procedures *de novo*, but also decide what compounds to prepare. The specification gives literally no guidance with regard to what the requirements for activity are i.e. which substituents would be preferred. See *Ex parte Herzog, Hershberg, and Coan*, 115 USPQ 195 (Bd. Pat. App. & Int. 1956) affirming the examiner, and stating "it becomes obvious that the expressions defining the organic acids used.........are inclusive of inoperative materials and go far beyond the adequately disclosed subject matter of the specification." And also *Ex parte DIAMOND,* 123 USPQ 167 (Bd. Pat. App. & Int. 1959) where the examiner was affirmed for a scope of enablement rejection, and the court stated:

"the specification contains 23 specific examples, but it will be noted that they are to the preparation of relatively simple compounds.........This must be regarded as a relatively meagre and nonrepresentative disclosure to support claims which embrace millions of compounds. It should also be observed that appellant is working in a field where little prediction is possible and this Board has on several occasions held that the scope of claims should not be unduly extensive in fields where applicability is highly speculative or not explored and that subject matter which relies upon prediction for its support is unpatentable. Ex parte Middleton, 87 USPQ 57 ; Ex parte Kauck et al., 95 USPQ 197 , Ex parte Rosenkranz et al., Pat. No. 2,715,637. In Minnesota Mining and Mfg. Co. et al. v. Carborundum Co. et al., 155 F.2d 746, 69 USPQ 288 , the court held that 'An inventor cannot disclose a small number of components which will serve as a springboard for claiming an entire class.'"

In addition *In re Fouche* 169 USPQ 429 dealt with a similar issue with respect to how to use requirement of 112 1st paragraph,

"Both the examiner and the board noted that none of the working examples pertained to compounds wherein Z was heterocyclic. Appellant is quite correct in contending that, under our decisions in In re Robins, 57 CCPA 1321, 429 F.2d 452, 166 USPQ 552 (1970), the inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention. Nevertheless, an applicant must use some technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art. It seems clear, and it is not disputed by appellant, that where an applicant undertakes to define his invention by the recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of the Markush group."

See also: *Schering Corporation v. Gilbert et al.*, 68 USPQ 84 (2d Cir. 1946)

"Theoretically a multitude of substances not as yet found in nature and not as yet compounded could be synthesized, if skilled organic chemists were given the time and materials with which to work, and actually the formulas for them could be written. There is, however, a practical limit upon synthesis, though the extent of that is not fully known, for some of the new theoretical compounds might be impossible to create, and some would be so unstable that they would disintegrate either at once or in short periods of varying length. Moreover, while analogy is at times useful, organic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected."

And *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976)

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

In re Prutton, 96 USPQ 147 (C.C.P.A. 1952)

"The complete list of organic compositions includes, in generic form, most of the organic compounds found discussed in ordinary textbooks of organic chemistry………. It appears to be appellant's view that a selection of an unsaturated hydrocarbon from the first list and of a sulphide of phosphorus from the second list will provide support for the claims here under discussion. The Examiner holds, and properly we think, that the presentation of such lists from which reagents may be selected is not a sufficient disclosure to support claims to a particular class of reaction product which might be produced by proper selection of reagents and determining the conditions of reaction."

In re Walker, 22 USPQ (C.C.P.A. 1934)

"It is true, as argued by counsel, that appellant is entitled to claim not only the substance enumerated by him in his specification, but also their equivalents. However, in cases of this character, involving chemicals and chemical compounds, many of which of course differ radically in their properties, it must appear in the specification, either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that "the chemicals or chemical combinations included therein were generally capable of accomplishing the desired result." See *In re Ellis*, 37 App. D. C. 203; *In re Dosselman*, 37 App. D. C. 211; *In re*

Langmuir, 20 C. C. P. A. (Patents) 733, 62 F. (2d) 93."

In Re Sus and Schaefer 134 USPQ 1962 301-310 (*affirmed*):

"It is, however, consistent with this public purpose embodied in the pertinent statutory requirement that the *invention claimed* shall be no broader than the *invention set forth* in the written description forming a part of the specification……thus it seems to us that one killed in this art would not be taught by written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only *certain aryl radicals* and certain specifically substituted aryl radicals would be suitable for such purposes." Emphasis in Original.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

David K. O'Dell

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